<u>REMARKS</u>

This Amendment and Response is submitted in response to the Notice of Noncompliant Amendment mailed from the U.S. Patent and Trademark Office on March 30, 2004. The Examiner noted that the amendments desired for Claims 1 and 39 were unclear. Accordingly, claims have been amended responsive to the Examiner's request. For the Examiner's convenience, Applicant has also herein re-presented Applicant's arguments filed in Applicant's Response to the Office action mailed on April 20, 2004, to which the present claim amendments correspond.

In the April 20, 2004 Office action, Claims 1-49 were pending. Claims 11, 12, 19, 23-38 and 41 were withdrawn from consideration. Claims 1-10, 13-18, 20-22, 39, 40, and 42-49 were rejected.

<u>IDS</u>

The Examiner makes reference to an Information Disclosure Statement filed on September 16, 2003. Upon a review of the FORM PTO-1449 returned with the Office action, it is apparent that the IDS was intended to be entered in Application Ser. No. 09/9<u>4</u>4,576, and not the present application having Ser. No. 09/9<u>2</u>4,576. Therefore, Applicant requests that the IDS be removed from the file.

<u>The Rejection under 35 U.S.C. § 101</u>

The Examiner has rejected Claims 1-10, 13-18, 20-22, 39, 40, and 42-49 under 35 U.S.C. § 101 because the claimed invention is allegedly directed to non-statutory algorithm type subject matter. In order to clarify the invention, Claim 1 has been amended to recite in new step c), determining the accuracy of the said plurality of biological markers in predicting said clinical endpoint; and in step d), identifying biological markers predictive of said clinical endpoint. Independent claims 39, 40, and 42 have been amended in an analogous manner. It is believed that the amendments are sufficient to overcome the rejection under 35 U.S.C. § 101. *See,*

Examination Guidelines for Computer-Related Inventions (Final Version), Section IV.2.(b).
Reconsideration is respectfully requested.

The Rejection under 35 U.S.C. § 112, second paragraph

The Examiner has rejected Claims 21 and 22 under 35 U.S.C. § 112, second paragraph, as
being indefinite for failing to particularly point out and distinctly claim the subject matter which
applicant regards as the invention. The second paragraph of Section 112 requires that the claims
set out and circumscribe a particular area which applicants regard as their invention with a
reasonable degree of precision and particularity. The test for definiteness under 35 U.S.C. 112,
second paragraph is whether "those skilled in the art would understand what is claimed when the
claim is read in light of the specification." *Orthokinetics, Inc. v. Safety Travel Chairs, Inc.*,
806 F.2d 1565, 1576, 1 USPQ2d 1081, 1088 (Fed. Cir. 1986).

Specifically, the rejection states that the phrase "desired computation time" causes the
claim to be indefinite because it is unclear what criteria is being used to determine that the
computation time is desirable. The rejection states that Applicant's example of support at
page 14, lines 17-24 [¶0039] was considered and found to be unpersuasive.

That paragraph reads as follows:

> The user-selected thresholds [applied in step **12**] can be derived based on a
> desired computation time. For example, the amount of time necessary to perform
> the subsequent step **14** can be determined empirically for a variety of data set
> sizes. In general, a formula for computation time cannot be determined, because
> of unknown processor-dependent factors, but the time can be determined
> empirically. The user can then select a desired computation time, and the required
> data reduction can be determined from the empirical results. The necessary data
> reduction determines the number of clusters m to select, which is an input to step
> **28** of FIG. 4.

The "computation time" is the amount of time necessary to perform the computation (i.e., the
"subsequent step **14**" as set forth in [¶0039]). The "desired computation time" is the computation
time desired by the user. The computation time in a given situation depends, *inter alia*, on

factors associated with the processor being used to perform the computation. As a simple example, the time required to perform the computations on a certain data set using a slow processor would be longer than the time required to perform the computations on the data set using a fast processor. For a given processor, computation time for a number of data set sizes can be determined empirically. The user can determine from such empirical results what amount of data reduction is necessary to allow the computation to be performed within the desired amount of time. The user-selected thresholds in step **12** can be set to achieve that amount of data reduction.

To illustrate, posit that the computation times for a hypothetical processor have been empirically determined to be as follows:

Data Set Size	Computation
200	10 minutes
500	25 minutes
1000	50 minutes
2000	100 minutes

The user may desire that the computation be performed in 25 minutes (the "desired computation time"). From these empirical results, the user could determine that the data set must be narrowed to at most about 500 and then select the thresholds to be applied in step **12** accordingly.

The rejection suggests that the "desired computation time"is indefinite because "said computation time can not be determined." To the contrary, the paragraph states that the computation time *"can be determined empirically"* as discussed above. Read in context, the phrase relied on by the Examiner states only that the present invention does not provide a formula from which computation time can be determined *a priori* because of unknown processor-dependent factors.

One skilled in the art would understand what is claimed when the claim is read in light of the specification; that is, a reading of the paragraph reproduced above, in the context of the disclosure of the specification clearly describes how to select a desired computation time. This

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language, therefore meets the requirements of 35 U.S.C. § 112, second paragraph.
Reconsideration is respectfully requested.

The Rejection under 35 U.S.C. § 112, first paragraph

The Examiner has rejected claims 1-10, 13-18, 20-22, 39, 40, and 42-49 under 35 U.S.C.
§ 112, first paragraph. The first paragraph of section 112 requires that a patent application be
written so as to "enable any person skilled in the art to which it pertains . . . to make and use the
same." A specification is presumed to be enabling absent "a reason to doubt the objective truth
of the statements contained therein." *In re Marzocchi*, 169 USPQ 367, 369 (C.C.P.A 1971).
Further, a specification "may be enabling even though some experimentation is necessary,"
United States v. Teletronics, Inc., 857 F.2d 778, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988), so long
as the amount of experimentation required is not "undue experimentation." *In re Wands*,
858 F.2d 731, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). The test is whether the specification
"provides a reasonable amount of guidance with respect to the direction in which the
experimentation should proceed." *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400, 1404 (Fed. Cir.
1988). Further, it is a tenet of patent law that an applicant need not teach what the skilled artisan
already knows. Instead, it is preferred that an applicant "omit what is known in the art."
Hybritech Inc. v. Monoclonal Antibodies, 231 USPQ 81, 94 (Fed. Cir. 1986). With this standard
in mind, the rejection raised by the Examiner are discussed below.

A.   The Rejection of Claims 47-49. Claims 47-49 have been rejected under 35 U.S.C.
§ 112, first paragraph, as containing subject matter which was not described in the specification
in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the
application was filed, had possession of the claimed invention. The rejection indicates this is a
new matter rejection.

The rejection indicates that the limitations of n being "1000 or more," "5000 or more" and "10,000 or more" are not supported by the specification, although 5000 and 1000 biomarkers are disclosed for 100 subjects. Applicant respectfully traverses this rejection.

Support for these limitations can be found at page 3, lines 7-9, page 8, lines 18-21, and lines 28-29. Page 3, lines 7-9, referring to Figure 1, states that "[i]t is not uncommon for hundreds or thousands of measurements to be acquired on samples from fewer than one hundred patients. "This clearly supports the limitations of "1000 or more," "5000 or more," and "10000 or more." Additionally, page 8, lines 28-29 indicate that "[i]t is not uncommon for between *five and ten thousand measurements* to be acquired for each of fewer than one hundred subjects," supporting the limitation of "5000 or more" and "10000." Finally, page 8, lines 18-21 indicate that "*n is much larger than the number of observations p* (e.g., biological samples or subjects in an experimental study). In a preferred embodiment, $n > 10p$." In this case, if p is 100, then n is greater than 10 x 100, or n is greater than 10,000. Thus, lines 18-21 provide support for n more than 10,000.

Reconsideration is respectfully requested.

B.   The Rejection of Claims 1-10, 13-18, 20-22, 39, 40, and 42-49. Claims 1-10, 13-18, 20-22, 39, 40, and 42-49 have been rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement, and as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The rejection alleges that the invention would require undue experimentation to perform. Applicant respectfully traverses this rejection, and responds to the statements in the rejection in turn.

1.   The rejection asserts that the level of skill in molecular biology is high, but that the "results of experiments in genetic engineering are unpredictable." The present claims are directed to methods for identifying biological markers and program storage devices, tangibly

embodying a program of instructions to perform method steps for the biological marker identification methods. The claims are not directed to "genetic engineering." Therefore, Applicant submits that the predictability or unpredictability of genetic engineering experiments is irrelevant to the present claims.

2.   The rejection asserts that no specific clinical endpoints are disclosed which have been identified using the claimed method as directed to any specific set of biomarkers, and that without any specificity as to the type of clinical endpoints or drugs, one of skill would not know how to predictably practice the claimed invention without undue experimentation. Claim 1 is directed to a "method for identifying biological markers in a set of n biological measurements for each of p observations, wherein $n > p$ and each observation is associated with a clinical endpoint." The later step of identifying biological markers predictive of <u>said</u> clinical endpoint, therefore, refers to the clinical endpoint associated with the original observations. Because the observations are already associated with a clinical endpoint prior to the identification, the claim is specific as to identifying biological markers predictive of that clinical endpoint. Independent Claims 39, 40, and 42 similarly refer to observations associated with a clinical endpoint, and identifying biological markers predictive of <u>said</u> clinical endpoint.

3.   The rejection states that the broad data sets of the present invention can include types of measurements, such as CD4 T-cells, and that "these types of measurements alone are not specific to any clinical endpoint or disease." The claimed invention, however, is not directed to "measurements of biomarkers alone." The claims instead are directed to a method and program storage device for identifying biological markers from observations wherein "each observation is associated with a clinical endpoint" and where the biological markers identified are associated with that clinical endpoint. The claims provide a novel series of steps that start with n biological measurements and result in the identification of biological markers by reducing the set of measurements, selecting markers from the reduced set, and determining the accuracy of the selected markers in predicting a clinical endpoint. The method has general applicability to any number of diseases and types of measurements (Specification, page 8, line 30 to page 9, line 2).

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However, it can not be said that the claims refer to "measurements of biomarkers alone" and therefore applicant submits that the rejection's assertion is irrelevant to the present claims.

4.   The rejection asserts that no specific biomarkers are disclosed to predict a clinical endpoint. It has been determined by the courts, that no working examples are required to enable a patent application. *In re Borkowski et al.*, 422 F.2d 904, 164 USPQ 642 (CCPA 1970). The presence of working examples is only one factor in the enablement determination. In the present application, the Applicant has provided a specification that details the steps necessary to identify biomarkers predictive of a clinical endpoint, and submits that working examples are not necessary for enablement in light of the detailed specification which would be understood by one of skill in the art. Moreover, the Examiner's remarks appear to assume that the claims are directed to biomarkers, rather than methods used to analyze data to identify biological markers.

Reconsideration is respectfully requested.

The Rejection under 35 U.S.C. § 102(e)

The Examiner has rejected Claims 1-7, 13, 16-18, 20-22, 39, 40, and 42-49 under 35 U.S.C. § 102(e) as being anticipated by Campell, et al., U.S. Patent No. 6,059,724 ("Campell, et al."). The Court of Appeals for the Federal Circuit has stated that anticipation requires the presence in a single prior art reference of each and every element of the claimed invention. *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1458 (Fed. Cir. 1984); *Alco Standard Corp. v. Tennessee Valley Auth.*, 1 U.S.P.Q.2d 1337, 1341 (Fed. Cir. 1986). "There must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention." *Scripps Clinic v. Genentech Inc.*, 18 U.S.P.Q.2d 1001, 1010 (Fed. Cir. 1991) (citations omitted).

Campell et al. describes a computer-based method for predicting the future health of individuals. According to the method, a set of biological measures is acquired from a large number of patients, each in one of two classes, and the measures are analyzed to locate biological markers capable of distinguishing between the classes. The number of markers to be considered

is progressively reduced, and a discriminate analysis is performed on the remaining measures to identify the biological markers. The biological markers can then be used to predict the risk of a person of acquiring a disease corresponding to one of the classes.

The Examiner points to a number of passages in Campell et al. and asserts that the disclosure anticipates the present claims. However, as explained below, Campell et al. does not teach the methods defined by the present claims.

The Examiner contends that the example of a training set provided in Campell et al. at column 33, lines 9-14 anticipates claim 1 of the present invention. In that example, Campell et al. describes a group of 481 patients that collectively made 641 annual visits for evaluation. Thus, not every subject made two annual visits and Campell et al. states that "not all biomarkers were assessed, even when a subject made a visit" (col. 33, line 11-12). Campell et al. does not disclose how many biomarkers were measured at each visit. However, the Examiner states that other disclosure in Campell et al. suggests the measurement of 36 biomarkers for sickle cell anemia as shown in Table 2. The Examiner reasons that for 641 annual evaluations from 481 subjects (1.3 annual evaluations/subject), "the number of biological measurements is at least 36 biomarkers x 641 evaluations or 23,076 biological measurements (n). The Examiner further reasons that the number of biological measurements is greater than p, which is 481 because there were 481 patients from whom samples were taken. See page 2, line 27. However, as used in the present application, n refers to the number of measurements made with respect to each patient/sample, not the number of total measurements for all patients (see paragraph 12, which begins: "[t]he present invention provides a method for identifying biological markers in broad data sets containing n biological measurements for each of p observations." (emphasis added)). The claims also reference n biological measurements for each of p observations. There is no basis for the calculation of n as 23,076 as reported by the Examiner. Making the most generous assumptions with respect to this example, you would assume that each of the 36 biomarkers was measured for each patient, and that each patient made both annual visits. Based on these assumptions, the number of measurements n would be at most 72 (i.e., 36 measurements on two

occasions). This does not anticipate the present invention because n (72) is not greater than p (481) as required by the pending claims.

The number of observations p can also be used to represent the number of samples (page 2, lines 25-26). Analyzed in this way, however, the data set is even "narrower" — the number of observations p would be no fewer than 641, making the favorable assumption that only one sample was taken from each patient at each visit. Under this definition of p, while using the assumptions most favorable to obtaining a broad data set, n (36) still is not greater than p (641) as required by claim 1.

Independent claim 39 requires an even "broader" data set (i.e., $n > 10p$). Campell et al. does not anticipate claim 39 for the same reasons it does not anticipate claim 1.

The rejection further asserts that n biological measurements is reduced to a set of m candidate measurements, and points to Table 2 as an example of m candidate measurements. The Examiner's assertion, however, that n is reduced to m, is inconsistent with the Examiner's (erroneous) calculation of n based on the 36 values in Table 2. Furthermore, Campell, et al. provides no basis to conclude that the total number of measurements obtained (n) was reduced to a set of candidate measurements (m) which the Examiner asserts are set forth in Table 2. Rather, what is set forth in Table 2 is a list of all demographic data, clinical chemistry data and hematological data that was collected for the patient (col. 33, lines 17-20). The category referred to as "Potential Biomakers" in Campell et al. is most analogous to the category referred to as "measurements" in the present application. Campell et al. does not disclose data sets in which $n > p$ or $n > 10p$ as required by the pending claims.

The rejection also states that Campell et al. discloses that each candidate biomarker in Table 2 represents a specific type of measurement and refers to this measurement as k. The rejection further states that "each measurement of each distinct biomarker k is less than p." However, as used in the present application, k does not denote "each measurement of each distinct biomarker." Rather, the present application teaches that a biomarker for a particular disease can consist of a number of biological measurements and k is used to denote that number

(page 9, lines 4-18; page 6, lines 18-25). The Examiner's further assertion that k is less than 128 is not supported by Campell et al.

As described above, Campell et al. does not anticipate the claims of the present application, at least because it does not disclose broad data sets where $n > p$, as required in the independent claims 1, 39, 40, and 42. The remaining assertions in the rejection under Section 102 are directed to limitations appearing in the dependent claims. Because Campell et al. does not anticipate independent claims 1, 39, 40, and 42, it can not anticipate any claim dependent therefrom.

Moreover, as more fully set forth in the present specification, the method of Campell et al. is directed to a qualitatively different problem from the method of the present claims. In Campell et al., the number of measurements must be reduced sufficiently in order to allow the discriminant analysis to be performed. This is why the number of measures is smaller than the number of samples. Additionally, in the method of Campell et al. significant domain knowledge is required to choose the original set of potential markers and to reduce the set. This domain knowledge does not come from the statistical techniques themselves — it must be supplied by experts in the field who have knowledge of the particular disease and of the biological factors already known to be important in that disease. This is in sharp contrast to the methods of the present invention which are directed to the problem of searching for markers not previously known to have any correlation with the disease of interest.

The Rejection under 35 U.S.C. 103(a)

The Examiner has rejected Claims 1-10, 13-18, 20-22, 39, 40, and 42-49 under 35 U.S.C. § 103(a) as being unpatentable over Campell, et al. U.S. Patent No. 6,059,724 taken with Perou, et al., *Nature* (2000) 406:747-752, in view of Lucas, et al., U.S. Patent No. 5,871,946. The Examiner bears the burden of establishing a prima facie case of obviousness (Section 103). In determining obviousness, one must focus on Applicant's invention as a whole. *Symbol*

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Technologies Inc. v. Opticon Inc., 19 U.S.P.Q.2d 1241, 1246 (Fed. Cir. 1991). The primary inquiry is:

> whether the prior art would have suggested to one of ordinary skill in the art that
> this process should be carried out and would have had a reasonable likelihood of
> success. . . . Both the suggestion and the expectation of success must be found in
> the prior art, not in the applicant's disclosure.

In re Dow Chemical, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988).

As described above, Campell et al. does not anticipate the claims of the present application, at least because it does not disclose broad data sets where $n > p$. The Examiner does not suggest that the secondary references disclose broad data sets where $n > p$ (and they do not). Rather, the Examiner cites the secondary references for their disclosure with respect to the limitations of correlation based on hierarchical cluster, user-selected correlation threshold and ranking of biological markers.

Eisen et al. relates to a system for cluster analysis of genome-wide expression data. It is an example of one of the current approaches to the computational analysis of gene expression data that attempts to learn functionally significant classifications of genes either in a supervised or unsupervised manner. The aim in Eisen et al. is not to locate specific features capable of classifying patients, but rather to cluster different genes into functional classes. Eisen et al. use hierarchical cluster analysis (HCA) to visualize genes' functional relationships. Based on the cluster trees obtained, a user can hypothesize new gene functional classes. Thus, as an initial matter, it is far from clear that one of ordinary skill in the art would be motivated to combine the disclosure of Eisen et al. with that of Campell et al.

The Examiner asserts that Eisen et al. discloses hierarchical cluster analysis [as] a type of correlation analysis that was used for analyzing a large data set as in instant claim 8. While Eisen et al. does refer to hierarchical cluster analysis, like Campell et al, it lacks a disclosure of broad data sets where $n > p$. Thus, even if combined, Campell et al. and Eisen et al. would not obviate the present claims.

The Examiner states that Lucas et al. discloses a method of studying biological surface markers and ranking cells by the functional activity of the cell markers as in instant claims 14 and 15. The first cited passage describes using flow cytometry to sort healthy and diseased cells. This is not a "method of studying biological surface markers." The second cited passage does not describe ranking cells by the functional activity of the cell markers; rather it describes classification of cells on the basis of enzyme activities. However, neither claim 14 nor 15 recite ranking or classifying <u>cells</u> — rather, both claims recite ranking <u>biological markers</u> (e.g., in dependence on their accuracy of predicting clinical endpoints). The type of ranking disclosed in Lucas et al. appears to relate to the differentiation of cells into various populations on the basis of intracellular enzymatic activity. This is much different than ranking biological markers based on dependence on accuracy of predicting clinical endpoints.

Moreover, Lucas et al. is directed to a method for determining the activity of an endogenous enzyme in a metabolically active whole cell. One of the uses of the method is to measure enzymatic activity in cells from different diseases. Thus, Lucas et al. is similar to Eisen et al., except that rather than genomic data, Lucas et al. is limited to intracellular enzyme activity. Both references create a data matrix that can then be analyzed with various statistical tests to identify patterns of enzyme activities. Thus, it is also far from clear that one of ordinary skill in the art would be motivated to combine the disclosure of Lucas et al. with that of Campell et al.

Lucas et al. do not relate method of efficiently mining broad data sets, that is, a data set in which $n > p$, which is required in the present claims. Indeed, Lucas et al. teaches using a small number of measurements. See, e.g., col. 43, lines 52-57 ("The selection of a relatively <u>small</u> <u>number</u> of components for the measurement vector is necessary to simplify the later analysis, reduce the number of physical measurements which must be made and to reduce the effects of spurious noise generated from the measurements and from individual variation among the same population" and then reducing that small number to those "contributing most to distinguishing different disease states" (emphasis added)). In addition, the standard statistical methods

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disclosed in Lucas et al. are inappropriate for analysis of broad data sets in which $n > p$. Thus, even if combined, Campell et al. and Lucas et at. would not obviate the present claims.

Closing Remarks

Based upon the foregoing, the Applicant believes that all pending claims are in condition for allowance and such disposition is respectfully requested. In the event that a telephone conversation would further prosecution and/or expedite allowance, the Examiner is invited to contact the undersigned.

Respectfully submitted,

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